Capillaries

Introduction

Within the capillaries is where all the stuff happens. Arteries carry blood to arterioles, arterioles control blood flow into the capillaries, some magic happens, then venules and veins bring blood away from the capillaries. We are going to discuss the magic in this lesson.

Capillaries are unique blood vessels in that they are **very small**—the smallest blood vessels—and have **no tunica adventitia or tunica media**. They are just a **tunica intima**, consisting of only **endothelium** and its basement membrane. The endothelium is only one endothelial cell thick. The endothelial cells surround a lumen filled with blood, just as all blood vessels do. What makes capillaries special is that fluid (water) and molecules/cells (stuff) can enter and leave the capillary.

In this lesson, **filtration** means the movement of **fluid** out of the capillary and into the tissue. Its inverse counterpart is **absorption**, the movement of **fluid** into the capillary and out of the tissue. **Diffusion** is the movement of **stuff**, either into the capillary out of tissue or into the tissue out of the capillary. "Stuff" can be anything—water, ions, peptides, lipophilic compounds, even entire cells.

We do diffusion first, discussing the arrangement of the arterioles and capillaries and the cells they service. We then discuss the different types of capillaries based on how well they restrict the diffusion of molecules and fluid. We provide a simplified, more clinical approach to the forces of filtration and absorption, then use those concepts to explore edema—fluid where fluid shouldn't be.

Capillaries and Diffusion

Capillaries service cells. They bring the cells **nutrients** and take away **waste**. Nutrients can be anything, any molecule or substance the cells could need, including oxygen, glucose, water, ions, and even peptide hormones. Waste is primarily carbon dioxide and hydrogen ions. For our discussion here, "molecule" is defined broadly—either nutrient or waste. We then use the diffusion equation to help understand how diffusion out of and into the capillary occurs and any consequences this may have for how capillaries are arranged around cells.

The diffusion equation has five parts: permeability (k), concentration gradient, surface area, diffusion barrier thickness, and molecular size. This is the diffusion equation from General Physiology and General Pharmacology.

First, we can remove permeability and size from our discussion. We are taking the movement of nutrients and waste as a given. If it can diffuse, it will diffuse. Second, the **concentration gradient** is **always favorable**. We have a circulatory system so that red blood cells (RBCs) can bring oxygen to the cells that are using oxygen. The cells use oxygen and produce carbon dioxide, which the RBCs take away. The point is, the cells will always need what RBCs bring (high concentration in the RBCs, low in the cells), and the cells will always generate byproducts of their metabolism (high concentration in the cells, low in the RBCs). Third, diffusion is improved with **decreased diffusion barrier thickness—**there is no tunica media or tunica adventitia, just the endothelium. Finally, the surface area correlates to the **number of capillaries**. Each arteriole gives rise to a number of capillaries (how many isn't important). Each capillary perfuses cells. The responsibility for that perfusion is split amongst capillaries. Each arteriole has its territory (the sum of all the capillaries), and each capillary has its own territory.

The arterioles become capillaries, which then converge into venules. That means the capillaries have a **length**. The cells that the capillary encounters first will extract nutrients from the capillary, leaving less behind in the capillary. The next cell will extract nutrients, and so on, and so on. By the venule end of the capillary, there are fewer nutrients than at the arteriolar end. An important consideration for this

fact is **oxygen**. The heart has 80% oxygen extraction, the highest in the body. Yet oxygen still leaves the heart in the coronary veins, demonstrating that the blood has inherent redundancy built in, always carrying more oxygen (the nutrient) than an organ will need, ensuring that every cell in the organ gets access to the nutrient.

The capillaries share territory. That means some cells are farther from a capillary than others. Not only must nutrients and waste products diffuse out of the capillary and into tissues, but also through or around the tissue's cells. This **distance** from the capillary has a similar effect to the length of the capillary. There are fewer nutrients further from the capillary than near it.

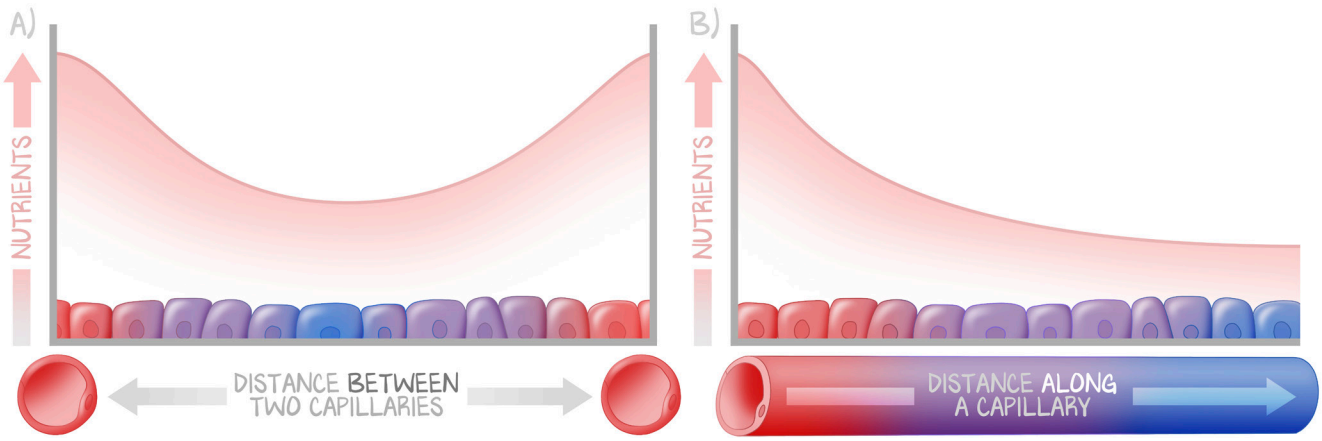

Figure 2.1: Function of Capillaries
(a) This illustration depicts the concentration gradient near capillaries, with both capillaries cut in cross-section. Nutrients are quickly consumed by the cells between capillaries. The cells that are equidistant between two capillaries receive the fewest nutrients. (b) This illustration shows the concentration gradient along the capillary length, shown in longitudinal section from capillary to venule. Cells at the head of the capillary take and use the oxygen in the blood, leaving progressively less oxygen to be used by cells the farther down the capillary blood travels.

You're going to have a stronger appreciation for this after the Gastrointestinal and Endocrine modules. There, nutrients and waste become an array of complex molecules, and cells farther along the vascular system will be influenced by the products of cells that come before it. This may seem abstract now, but it will become more concrete.

Types of Capillaries

Capillaries are the smallest blood vessels and the site of nutrient and gas exchange with tissues. The walls are the thinnest of any of the blood vessels, existing only as a simple squamous epithelium (the endothelium) atop a basement membrane. There are three types of capillaries, categorized by how tight a seal they make: continuous, fenestrated, and sinusoidal. Take a look at Figure 2.2 to get started, then we'll go over the details of each type.

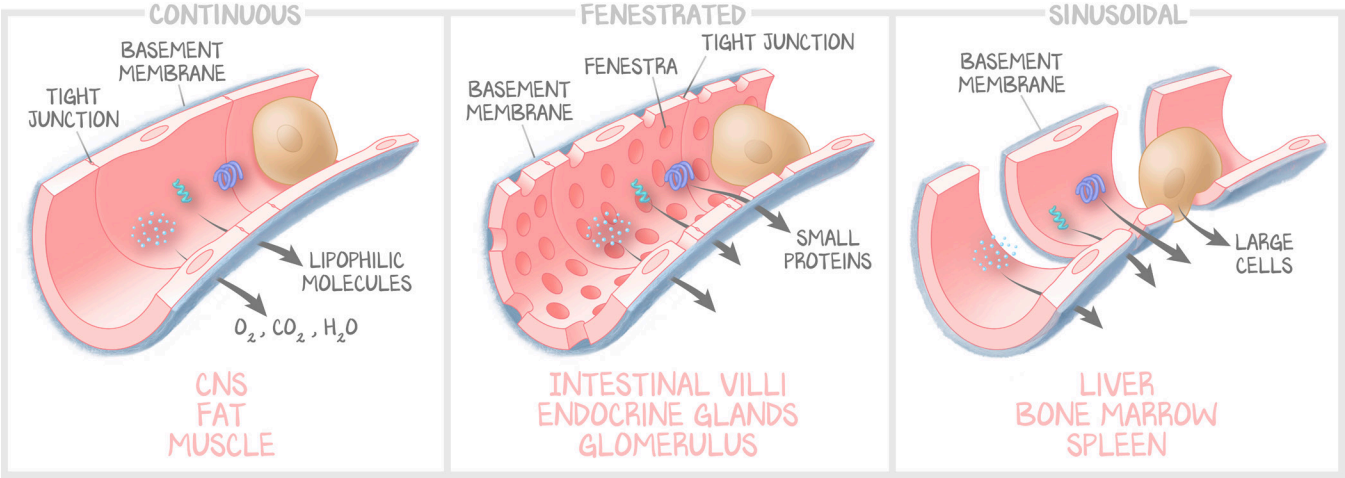

Figure 2.2: Capillaries and Diffusion
Capillaries come in three varieties: continuous, fenestrated, and sinusoidal. Continuous capillaries block filtration, allowing only lipophilic or very small molecules (oxygen, carbon dioxide, water) out of or into the lumen. Fenestrated capillaries have fenestrae, which allow small molecules, such as hydrophilic peptides, through them, but the gaps are so small that only protein-sized molecules can exit, whereas cells remain trapped in the lumen. Sinusoidal capillaries have such large gaps between endothelial cells that there is not even a basement membrane. Nothing, not even cells, is restricted from exiting the lumen of sinusoidal capillaries.

Continuous capillaries are designed to **separate compartments** and **prevent the passage** of molecules from one compartment to another. The **blood-brain barrier**, blood-testis barrier, and maternal-placental barrier are prime examples. The endothelial cells adhere to one another tightly via **tight junctions** (zona occludens), leaving no space for molecules to exit. Only those molecules that can diffuse through a plasma membrane can exit—water, oxygen, carbon dioxide, and **lipophilic compounds** can exit the lumen into the surrounding tissue. There are no fenestrations and no gaps between cells.

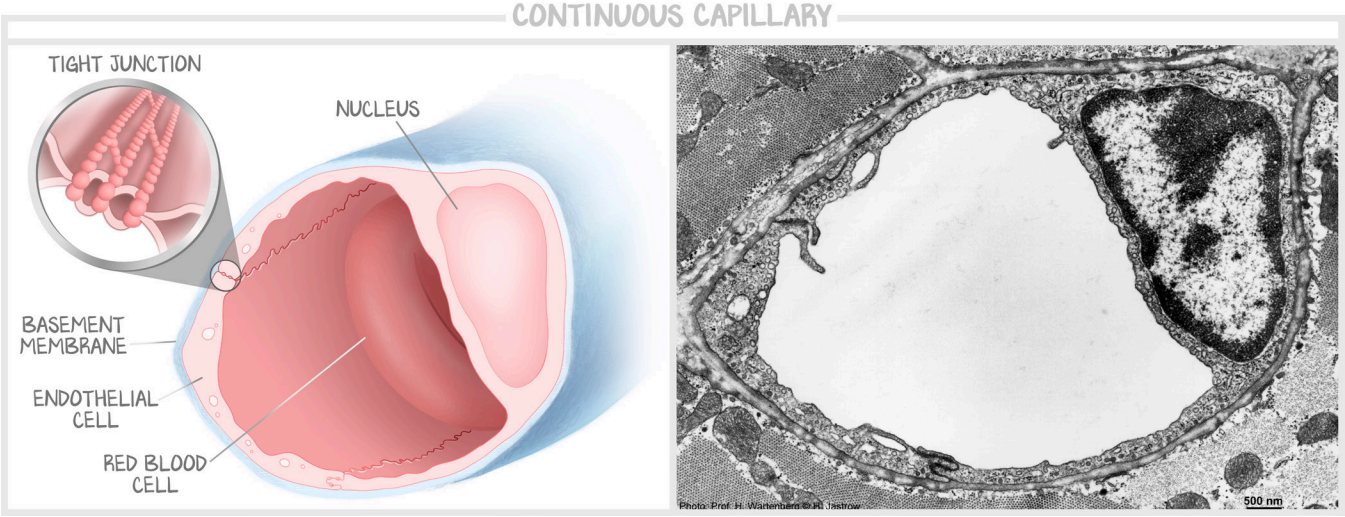

Figure 2.3: Continuous Capillaries

Fenestrated capillaries permit the diffusion of small hydrophilic molecules, such as peptides. Any cell that receives a peptide hormone signal or releases a peptide hormone requires fenestrated capillaries to let the peptide hormone into or out of the cells' extracellular matrix. Fenestrations permit filtration

in the glomerulus of the kidney (filtration meaning both stuff leaving the capillary and literal filtration of the blood). Fenestrated capillaries consist of endothelial cells that hold on to one another via tight junctions, just like continuous capillaries, so there are no gaps between cells. The basement membrane is continuous (although it does not restrict the movement of small peptides or ions). Littered throughout the endothelial cells are **fenestrations** (also called fenestrae or pores), gaps in the plasma membrane. These channels represent where an endothelial cell isn't. The endothelial cell has a plasma membrane that contains its cytoplasm. The fenestrations are lined with a plasma membrane that is continuous with the plasma membrane of the endothelial cell's surface on the capillary lumen side and the endothelial cell base on the basement membrane side.

There is a scene in Disney's *The Little Mermaid* that conveys this well. Toward the end, Ursula has the trident of power, has grown to gigantic proportions, and begins to stir the sea. She traps mermaid Ariel at the bottom of the sea. But Ariel is in a column of air, connected to the sky, the ocean swirling around her. Ariel is lying on the seafloor, now also exposed to air. Ariel is a large protein, the seafloor is the basement membrane, the swirling ocean around her is the plasma membrane of the endothelial cell, the column of air is the fenestra, the sky above the surface of the ocean is the lumen of the capillary, and the ocean surface is the luminal plasma membrane. https://www.youtube.com/watch?v=N7k9KFGLg_U (free on YouTube at minute 1:30)

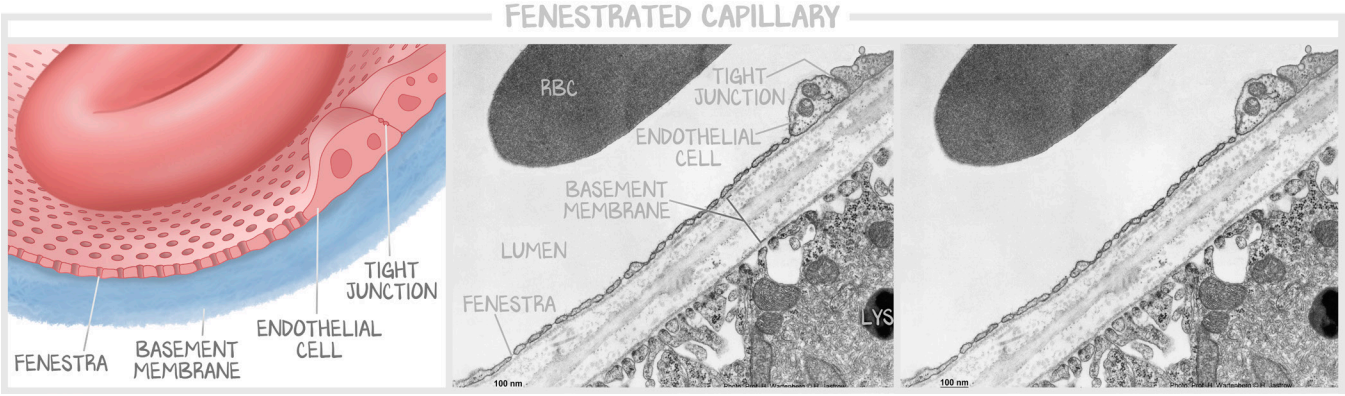

Figure 2.4: Fenestrated Capillaries

Sinusoidal capillaries are used in the "reticuloendothelial system" (a complicated way of saying hematopoietic organs, which is a complicated way of saying the **liver**, **spleen**, and **bone marrow**). Sinusoidal capillaries have **gaps between endothelial cells** that are large enough to let out whole cells. Gaps between cells means a **discontinuous epithelium** and with it a discontinuous basement membrane. Wherever an endothelial cell is, a basement membrane will be, too. Wherever an endothelial cell is not, a basement membrane will not be. Basement membranes can restrict cells. Without a basement membrane or an endothelial cell to prevent it, cells (whether host cells or pathogens) can not only leave the organ into the blood vessels but also leave the blood vessels into the organ. Thus, in the absence of any ability to filter what leaves the vessel, sinusoidal capillaries often have resident macrophages—Kupffer cells—within the lumen or standing in place of an endothelial cell as part of the capillary endothelium. There are other purposes for sinusoidal capillaries, but we want the image of cells exiting to stick, showing how much larger the gaps are between cells in the sinusoidal capillaries than the fenestrations of fenestrated capillaries.

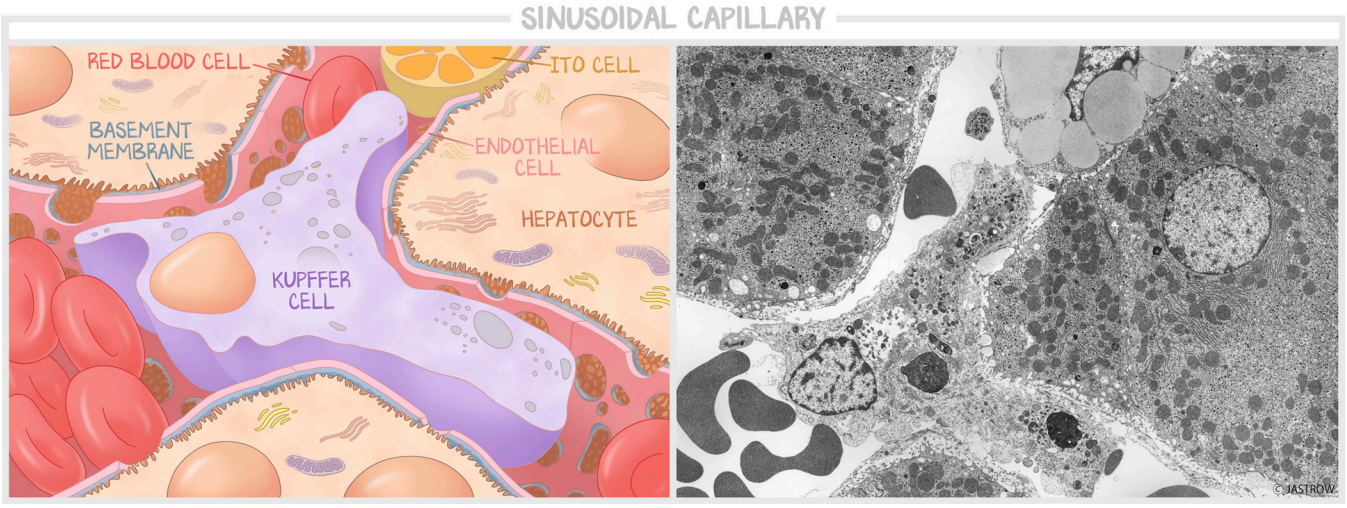

Figure 2.5: Sinusoidal Capillaries

Capillaries, Filtration, and Absorption

Filtration and absorption are interrelated with diffusion. Both molecules and fluid can be filtered and absorbed. We stress the distinction between diffusion of stuff (molecules) and filtration of fluid to keep the components separate in your brain. Filtration of fluid in all capillary beds sets us up for the symptom of edema—fluid where fluid should not be. So this next discussion is about the forces of filtration and absorption that move fluid.

There are two compartments: one within the capillary lumen, designated the **capillary compartment**, and one outside the lumen, within the interstitial space between the cells of the capillary, designated the **interstitial compartment**. There are two forces: **hydrostatic** forces that push, traditionally represented by **P**, and **oncotic** forces that pull, represented by π. The hydrostatic pressure pushes fluid, either into the interstitium from the capillary or into the capillary from the interstitium. Therefore, the hydrostatic forces oppose one another. Oncotic pressure pulls fluid either into the capillary from the interstitium or from the capillary into the interstitium. Therefore, the oncotic forces oppose one another. The net of these four forces—capillary hydrostatic, interstitial hydrostatic, capillary oncotic, and interstitial oncotic—is the direction the fluid moves—positive means out of the capillary and negative means into the capillary.

And that's where this equation comes from: $J = k\,[(P_{cap} - P_{int}) - (\pi_{cap} - \pi_{int})]$

What this says is that the hydrostatic pressures (P_{cap} and P_{int}) compete, the oncotic pressures (π_{cap} and π_{int}) compete, and fluid will only move if permeability (k) allows it. **This is not the equation to learn.**

Except for ascites (for which a diagnostic paracentesis will be performed) and obstructive uropathy (for which the complexity of this equation doesn't help), the **interstitial forces are negligible and so don't count**. You should learn the simplified version of this equation instead (Figure 2.6). Then we can start talking hydrostatic and oncotic pressures, using only the capillary pressures to discuss physiology and pathology.

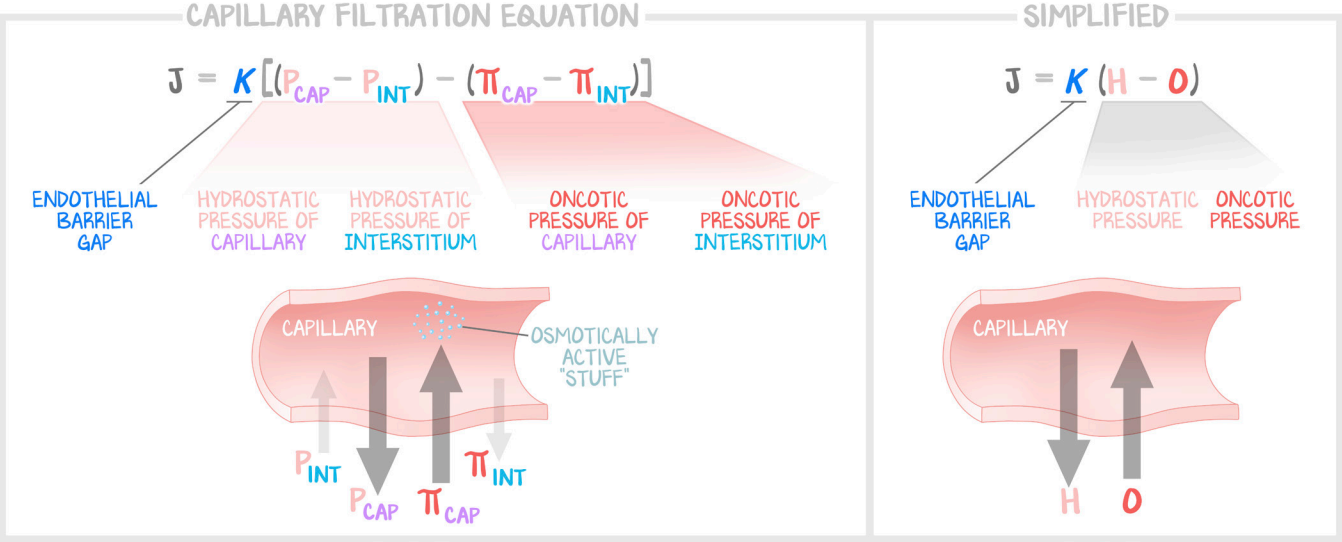

Figure 2.6: "J Equals"
This is one of the fundamental equations of pathophysiology and can be used to explain edema—fluid where fluid shouldn't be. In the Intern Content, we present "J equals snowman," a simplified version of this equation used for clinical applications. In Nephrology, this same equation is used to explain the glomerular filtration rate, effects of the afferent and efferent arterioles, and pathophysiology of nephrotic syndrome. It is easy once you know it. It is also sometimes daunting the first time it is encountered. You must know that there is a push force (hydrostatic) from the interstitium and the capillary. You must know that there is a pull force (oncotic) from the interstitium and the capillary. But because the interstitial forces are so weak, they can essentially be ignored. This simplifies the equation to three variables: the hydrostatic pressure in the capillary (H), the oncotic pressure in the capillary (O), and the vascular permeability (*k*).

The Movement of Fluid Changes Across the Capillary Bed

What creates the oncotic pressure is what the capillaries restrict the movement of—cells and large proteins, namely **albumin** and **red blood cells**. Because cells and large proteins are restricted from diffusing, their concentration doesn't change (accept this as true and the rest is easy; we don't want to get lost in the weeds). The assumption is that **oncotic pressure doesn't change** across the length of the capillary. Because we're on a progressive track of (appropriate) simplification, that means the hydrostatic pressure is what changes. And indeed, **hydrostatic pressure does change** across the length of the capillary.

The perfusion pressure through the arteriole into the capillaries pushes blood forward. But just like the forward pressure from the ventricle distends the large elastic arteries, so too does the perfusion pressure have a "distending force" in the capillary. The arterioles silence variability—there are no swings with each systole or diastole—but there is still a distending force from the incoming perfusion pressure. That distending force **is the hydrostatic pressure**. The perfusion pressure is kept at a MAP of around 90. The arterioles rank it down to around 10. On the arteriolar side, the capillaries start with 10 units of pressure. As with nutrients, this pressure is greatest at the beginning, diminishing along the capillary length. It will be used for filtration, to push fluid out of the capillaries. But because the perfusion pressure is so low, the hydrostatic pressure runs out by the venule end.

The oncotic pressure does not change. The hydrostatic pressure is exhausted across the length of the capillary. The only two forces that matter are the capillary hydrostatic pressure and the capillary oncotic pressure. At the start of the capillary, the arteriolar side, the hydrostatic force is the greatest, and the most fluid is pushed out of the capillary into the tissue. **Filtration wins** on the arteriolar side of the capillary because the hydrostatic force is greater than the oncotic force. At the end of the capillary, the venule side, well after the hydrostatic force has been exhausted and fallen below the oncotic pressure, the most fluid is pulled back in. **Absorption wins** on the venular side of the capillary because the oncotic pressure is greater than the hydrostatic force. Somewhere along the way, filtration becomes absorption.

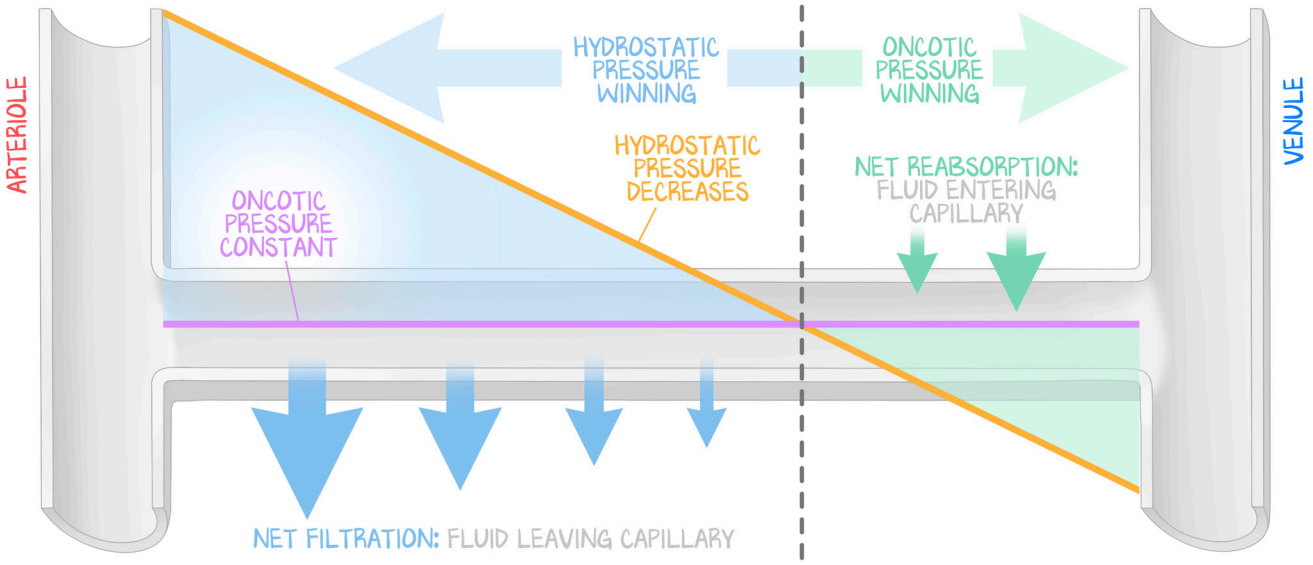

Figure 2.7: Forces Change Along the Capillary
On the arteriolar side, the greatest amounts of nutrients arrive with the greatest hydrostatic pressure. This leads to fluid rich in nutrients being pushed out into the tissues to nourish the cells. On the venular side, there is no hydrostatic force, only oncotic force pulling fluid in. Fluid from the tissue is rich in waste from the cells closest to the venule that will take the waste-filled blood back to circulation to be renewed with nutrients and hydrostatic pressure for its next pass.

Fluid Out Is Both Veins and Lymphatics

The discussion of fluid in/fluid out usually revolves around arteries and veins. The arteries bring the blood to the tissue AND supply the hydrostatic pressure to filter the fluid through the capillaries. The veins couldn't remove all the fluid on their own. They don't translate that pressure into forward velocity like the arteries do. All of the ventricular pressure has dissipated by the time the blood reaches the venous system. Gravity makes it harder for venous return to reach the heart from the lower extremities. The veins below the heart also contend with the column of blood above them. If there is excess fluid leaking out, the most likely place to find **edema is in dependent regions**. Dependent regions are the feet in people who can stand and the buttocks and sacrum in people who cannot get out of bed.

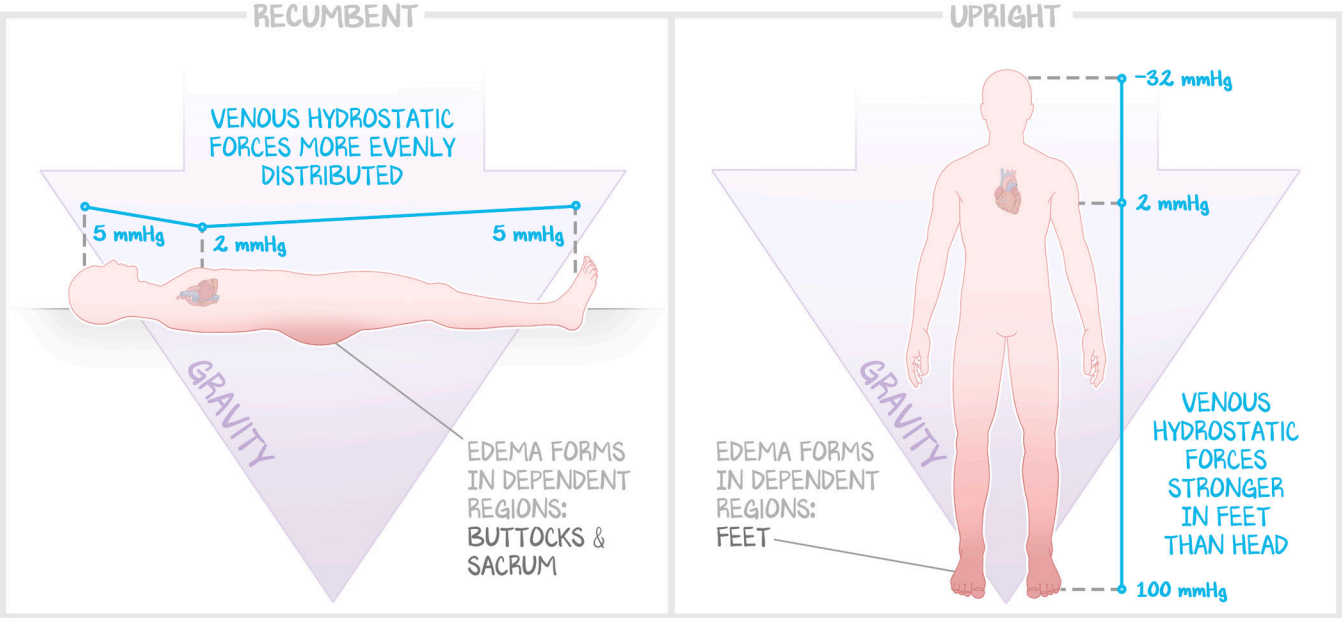

Figure 2.8: Gravity and Hydrostatic Forces
While recumbent (lying flat), gravity affects all capillary beds more evenly because the weight of the body isn't over them. When upright, gravity pulls down, enabling the return of blood from the head and neck but preventing the return of blood from below the heart without active pumping. In addition, when there is excess fluid, the column of fluid in the veins provides a hydrostatic pressure that prevents absorption in the veins.

The body relies on the **contraction of the skeletal muscles** to push the blood along the veins. The skeletal muscles, not the heart, force the blood to return to the heart. The contraction of skeletal muscles shmooshes the veins. This would push the fluid in both directions—up and down—if it weren't for valves. One-way **valves** exist in veins to prevent gravity-induced backflow of blood into the periphery once the muscles have contracted it toward the heart. Another factor that helps return blood to the heart is **thoracoabdominal pumping**. When you inhale, the thoracic pressure becomes negative, and air is sucked into your lungs. But the force isn't just on the air. The same sucking force is applied to the veins. Decreasing the thoracic pressure to an effective vacuum pulls air into your lungs and blood into your heart. This is why the Valsalva maneuver is useful in assessing heart murmurs. The Valsalva maneuver increases thoracic pressure and reduces preload. Normal respiration is a less severe form of that maneuver that naturally improves venous return.

But the veins aren't enough. Every heartbeat brings more fluid into the capillary bed and forces more fluid out into the interstitium. The rate of venous removal just cannot keep up with arterial delivery. So the body uses a second system to get the fluid out—the **lymphatics**. The lymphatics connect secondary lymphoid organs, allowing antigen-presenting cells to circulate through antigen-sensing lymphocytes. The lymphatics are also the fluid removal network, connecting to the systemic circulation at the azygos vein, connecting back to systemic circulation as venous return. Lymphatics also rely on the contraction of skeletal muscle and thoracoabdominal pumping to circulate both cells and fluid.

The combination of both the lymphatics (a low-pressure system) and veins (also a low-pressure system) ensures the drainage of the fluid provided by the arteries (a high-pressure system).

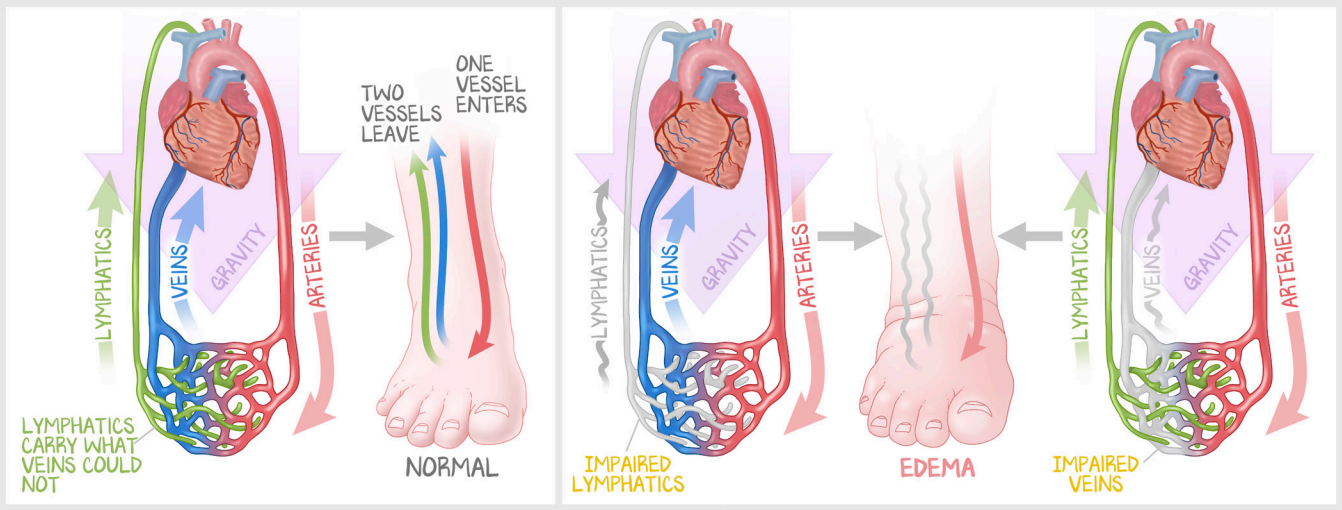

Figure 2.9: One Vessel Enters, Two Vessels Leave
Arteries bring blood into the tissues. Capillaries filter fluid into the tissues. Because gravity pulls fluid down and there is no perfusion pressure in the veins (other than skeletal muscle contraction), the veins must contend with gravity to reabsorb the fluid. Excess fluid is taken up by the lymphatics. If either the veins or lymphatics are compromised, the other cannot take up the slack, and fluid develops in the interstitial spaces, producing edema. Alleviating gravity (lifting the foot above the heart) can help the edema drain. (Easter egg: the title of this figure is a play on *Mad Max Beyond Thunderdome*, "Two men enter, one man leaves.")

Fluid Where Fluid Shouldn't Be: Edema

This final bit harnesses "J equals" and explains the content again, this time with a clinical approach. How much fluid moves is proportional to the magnitude of J. The direction that fluid moves is determined by the sign on J. If J is positive, fluid moves out of the vessel. If J is negative, fluid moves in. Edema is excess fluid in the interstitial space. See Intern Content: *Approach to Edema* for a more clinical application of this concept.

The permeability of the capillary is signified by ***k***. Sinusoidal capillaries have a very large *k*; tight capillaries have a very small *k*. But *k* can be changed. When you bang your knee, you get a red, hot, swollen knee. The swelling comes from inflammatory mediators that **increase the vascular permeability** of the localized tissue. The same thing happens in ARDS. Fluid leaks out into the interstitial space, resulting in pulmonary edema. The fluid leaks out because of the systemic inflammatory response syndrome—inflammatory mediators lead to vasodilation.

Capillary hydrostatic pressure can increase, NOT because of more arterial pressure, but because of more venous pressure. Gravity adds the weight of the column of blood in the veins above, pushing the fluid back out. Deep vein thrombosis prevents blood flow through a vein, and because the lymphatics and veins are already being used, the loss of a vein causes an accumulation of fluid and, therefore, pressure. Heart failure is the ultimate source of backpressure. If the heart pump breaks, every vein behind the pump feels increased hydrostatic pressure.

Capillary oncotic pressure is synonymous with albumin. In diseases that cause low albumin, the ability of the venule side of the capillary to draw fluid back into the capillary is reduced. This happens everywhere, resulting in global edema. We refer to reduced oncotic pressure collectively as the "Osi." Cirrhosis causes low albumin because the liver synthesizes albumin. Nephrotic syndrome ("nephr-osis") causes the spilling of albumin in the urine. Malnutrition ("gastr-osis") is insufficient protein-calorie intake to make enough albumin.

Interstitial oncotic pressure very rarely happens. When the oncotic pressure of the interstitium causes edema, it usually means something bad—bacterial infection, tuberculosis, or malignancy. These conditions generally cause "edema" in only two places—the thorax, where edema is called a pleural effusion, and the abdomen, where edema is called ascites.

Interstitial hydrostatic pressure essentially doesn't change. You should not learn any diseases in which this is a thing. Backpressure is felt at a macro level—tamponade of a bleeding vessel when an artery in the forearm fills the forearm so much that there is extreme pressure.